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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/696,016	10/29/2003	Ralph A. Casale	BP0206US-CN1	7084
23544	7590	12/01/2006	EXAMINER	
APPLIED BIOSYSTEMS 500 OLD CONNECTICUT PATH FRAMINGHAM, MA 01701			LUNDGREN, JEFFREY S	
		ART UNIT	PAPER NUMBER	
			1639	

DATE MAILED: 12/01/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)
	10/696,016	CASALE ET AL.
	Examiner Jeff Lundgren	Art Unit 1639

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 31 July 2006.
- 2a) This action is FINAL. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 28,41 and 75-96 is/are pending in the application.
- 4a) Of the above claim(s) 78,79,81,85,86,91,92 and 94-96 is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 28,41,75-77,80,82-84,87-90 and 93 is/are rejected.
- 7) Claim(s) _____ is/are objected to.
- 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on 29 October 2003 is/are: a) accepted or b) objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) All b) Some * c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____. |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>see Office Action</u> . | 6) <input type="checkbox"/> Other: _____. |

DETAILED ACTION

Election/Restrictions and Status of Claims

Applicant's election with traverse of species requirement in the reply filed on July 31, 2006, is acknowledged. The traversal is on the grounds that a species requirement may not be made within a specific claim. Applicants also cite certain court decisions without any analysis and comparison of the instant facts.

This is not found persuasive because this is simply not the standard for a species requirement. See 37 C.F.R. § 1.146.

Regarding the court's decisions on species, the M.P.E.P. summarized the decisions as follows:

"Since the decisions in *In re Weber*, 580 F.2d 455, 198 USPQ 328 (CCPA 1978) and *In re Haas*, 580 F.2d 461, 198 USPQ 334 (CCPA 1978), it is improper for the Office to refuse to examine that which applicants regard as their invention, unless the subject matter in a claim lacks unity of invention. *In re Harnisch*, 631 F.2d 716, 206 USPQ 300 (CCPA 1980); and *Ex parte Hozumi*, 3 USPQ2d 1059 (Bd. Pat. App. & Int. 1984). Broadly, unity of invention exists where compounds included within a Markush group (1) share a common utility, ***and*** (2) ***share a substantial structural feature essential to that utility***"

M.P.E.P. § 803.02 (emphasis added).

In the instant case, none of the members of each respective class of the four species share a substantial structural feature essential to the claimed utility. The requirement is still deemed proper and is therefore made FINAL.

Claims 28, 41 and 75-96, are pending in the application. Claims 78, 79, 81, 85, 86, 91, 92 and 94-96, are withdrawn as being directed to non-elected species. Claims 28, 41, 75-77, 80, 82-84, 87-90 and 93, are the subject of the Office Action below.

Objection to the Abstract Under 37 C.F.R. § 1.72

The abstract of the disclosure is objected to because it does not allow the public generally to determine quickly from a cursory inspection the nature and gist of the invention. Applicants should amend the abstract so that it corresponds to at least one independent claim. For example, Applicants should describe the steps of a) through e) in either claim 28 or claim 41. *See*

37 C.F.R. § 1.72. Should Applicants amend the claims in their next reply, the amended abstract should take into account any further limitations added to the broadest independent claim.

Information Disclosure Statement

The information disclosure statements (IDSs) submitted on August 8, 2004, August 11, 2005, and April 17, 2006, have been considered by the Examiner. The submission is in compliance with the provisions of 37 CFR § 1.97. Enclosed with this Office Action is a return-copy of the Form PTO-1449 with the Examiner's initials and signature indicating those references that have been considered.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 28, 75-77, 80 and 82-84, rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 28, and all dependent claims, are rejected for reciting the phrase “*substantially removes the base labile N-terminal amine protecting group*” because it is not clear how a molecular substituent is “substantially removed,” comparison to being “removed” or “not removed.”

Claim 28 is indefinite for reciting “the base labile N-terminal amine protecting group” because this particular wording of the phrase does not have antecedent basis in the claim. Correction is required.

Claim 28 is indefinite for reciting the phrase “as soon as is practical” because one of ordinary skill in the art would not be able to determine the metes and bounds of this limitation. Neither the specification nor the relevant art teaches what is considered “practical” and what is not considered “practical,” and further how long would one consider the appropriate time to determine practicality.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. § 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness..

Claims 28, 41, 77, 80, 82-84, 87-90 and 93, are rejected under 35 U.S.C. § 103(a) as being unpatentable over Breipohl *et al.*, U.S. Patent No. 6,121,418, issued on September 19, 2000, in view of Kovacs *et al.*, Fourth International Electronic Conference on Synthetic Organic Chemistry (ECSOC-4), www.mdpi.org/ecsoc-4.htm, September 1, 2000, and Thomson *et al.*, *Tetrahedron* 51:6179-6194 (1995), and Koch *et al.*, *J. Peptide Res.* 49:80-88 (1997).

Claim 28 is directed to A method for forming a support bound PNA dimer, said method comprising: a) coupling a first PNA monomer to a sterically hindered solid support comprising a sterically hindered acid forming cleavable linker wherein the PNA monomer comprises a N-terminal amine base labile protecting group; b) optionally washing the solid support to remove excess first PNA monomer; c) treating the solid support for a period of about 1 to about 2 minutes with a deprotection reagent that substantially removes the base labile N-terminal amine protecting group from the support bound first FNA monomer but that does not allow for more than 50 percent cyclization and elimination of the first PNA monomer from the support; d) washing the solid support to remove the deprotection reagent; and e) coupling a second PNA monomer to the N-terminal amine of the first PNA monomer as soon as is practical after performing steps (c) and (d).

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Breipohl teaches a method for synthesizing PNA oligomers on a solid support, wherein the PNA monomer comprises a N-terminal amine base labile protecting group, and the solid support is a rink-type resin (col. 5, lines 25-26, in reference to prior art disclosure H. Rink, *Tetrahedron Letters* 1987, 3787-3790).¹ The group in Rink meet the limitations of the sterically hindered acid forming cleavable linker, and the trityl chloride resin of claim 82, 83 and 84 (regarding claim 84, Breipohl's commercially available resin, such as the Rink resin, provides greater than 0.08 mmol per gram); also meets the limitations of claim 93. Breipohl also teaches treating the solid support with deprotection reagents:

"Examples of reagents for eliminating the base-labile amino protecting group PG are a solution of piperidine, morpholine, hydrazine or 1,8-diazabicyclo[5.4.0]undec-7-ene (**DBU**) in diisopropylformamide, N-methylpyrrolidinone (**NMP**), acetonitrile (ACN) or dichloromethane (DCM); the use of 20% piperidine in DMF or N-methylpyrrolidinone and also of a mixture of 2% **DBU** and 2% piperidine in DMF or 0.1M DBU in DMF or 0.1M DBU in dichloromethane is particularly preferred for the Fmoc, Dnpeoc and Bnpeoc protecting groups."

Breipohl, col. 7, lines 22-33 (emphasis added). Accordingly, the limitations of claim 80 are taught. Breipohl also teaches the coupling of subsequent PNA monomers, *i.e.*, oligomers (col. 1, lines 28-32). Breipohl also teaches a number of base labile protecting groups, such as Fmoc and Bnpeoc (Breipohl, col. 6, lines 1-15).

Breipohl also teaches using acid labile protecting groups, as in claim 41:

Protecting groups which are compatible with the base-labile amino protecting group PG, such as, for example, protecting groups, which are *labile to weak or medium strength acids, of the urethane type, such as tertbutyloxycarbonyl (Boc), 4-methoxybenzyloxycarbonyl (Moz) or 3,5-*

¹ Since Rink is effectively incorporated by reference, in particular the teachings as it pertains to PNA suitable resin supports, Breipohl is treated as teaching these limitations. See, *Advanced Display Systems Inc. v. Kent State University*, 54 USPQ2d 1673 at 1679 (Fed. Cir. 2000) – "Incorporation by reference provides a method for integrating material from various documents into a host document --a patent or printed publication in an anticipation determination-- by citing such material in a manner that makes clear that the material is effectively part of the host document as if it were explicitly contained therein. See *General Elec. Co. v. Brenner*, 407 F.2d 1258, 1261-62, 159 USPQ 335, 337 (D.C. Cir. 1968); *In re Lund*, 376 F.2d 982, 989, 153 USPQ 625, 631 (CCPA 1967). To incorporate material by reference, the host document must identify with detailed particularity what specific material it incorporates and clearly indicate where that material is found in the various documents. See *In re Seversky*, 474 F.2d 671, 674, 177 USPQ 144, 146 (CCPA 1973) (providing that incorporation by reference requires a statement "clearly identifying the subject matter which [page 1680] is incorporated and where it is to be found"); *In re Saunders*, 444 F.2d 599, 602-03, 170 USPQ 213, 216-17 (CCPA 1971) (reasoning that a rejection for anticipation is appropriate only if one reference "expressly incorporates a particular part" of another reference).

dimethoxyphenyl-2-propyl-2-oxycarbonyl (Ddz), or of the trityl type, such as triphenylmethyl (Trt), (4-methoxyphenyl)diphenylmethyl (Mmt), (4-methylphenyl)-diphenylmethyl (Mtt), di-(4-methoxyphenyl)phenylmethyl (Dmt) or 9-(9-phenyl)xanthenyl (pixyl) are used for protecting the exocyclic amino function in the nucleotide bases B' which are protected in their exocyclic amino function. The use of butyloxycarbonyl (Boc), triphenylmethyl (Trt), (4-methoxyphenyl)diphenylmethyl (Mmt), (4-methylphenyl)diphenylmethyl (Mtt) or di-(4-methoxyphenyl)phenylmethyl (Dmt) is particularly preferred, with Trt, Mtt, Mmt and Dmt surprisingly effecting a marked improvement in the solubility of the monomers. The use of (4-methoxyphenyl)diphenylmethyl (Mmt) is very particularly preferred."

Breipohl, col. 7, lines 3-23 (emphasis added). As in claims 87-89, Breipohl also teaches benzyloxycarbonyl (*i.e.*, Bhoc or Z; col. 12, line 63), and teaches t-boc (*i.e.*, Boc), Mmt and Fmoc, and suggests that these groups may be used in many combinations for protection. As in claim 90, Breipohl suggests the nucleobase adenine and cytosine.

Breipohl does not explicitly state that a period of about 1 to about 2 minutes is the time for deprotection to avoid cyclization.

Kovacs teaches a method of synthesizing PNA oligomers on a solid phase. As part of the method, Kovacs teaches the removal of the N-terminal amine protecting group in about five minutes (see Scheme 2). Kovacs teaches coupling a first PNA monomer to a solid support (NovaSyn hydroxy-Tentagel resin) comprising an acid forming cleavable linker, wherein the PNA monomer comprises base labile N-terminal protecting groups (*i.e.*, Boc/Z and Fmoc/Z).

Thomson teaches PNA oligomer synthesis on resins. Thompson teaches a deprotection step that is carried out at 3 x 5 minutes.

Koch teaches that when using protected amines in PNA chemistry, careful selection of the base reaction conditions must be taken into consideration to avoid cyclization (first and second columns on page 80).

One of ordinary skill in the art would have had a reasonable expectation of success in arriving at the invention as claimed because each of Breipohl, Kovacs, Thomson and Koch are related to methods for preparing PNA oligomers on solid phases in a step wise manner, wherein the PNA monomers are added to the resin in protected form, followed by a deprotection step. The N-terminal base labile protecting groups of Breipohl and Kovacs are similar, and in some

instances, both teach Fmoc, a protecting group that each teaches can be removed with piperidine in DMF, as well as the use of other deprotection reagents. Although Kovacs teaches 5 minutes in Scheme 2, one of ordinary skill in the art would have recognized from the teaching of Kovacs that deprotection times of this type typically require a couple minutes to complete, and are parameters that are routinely adjustable. Such an understanding is evidenced by Koch and Thomson, (see Koch, page 81, col. 1, lines 1-20; and page 81, col. 2, lines 10-15, wherein 3 minutes are taught; see Thomson on page 6192, last paragraph). Absent any secondary considerations of nonobviousness, the limitation of about 1 to 2 minutes is an obvious variation of the times taught by Kovacs and/or Koch, and is considered routine experimentation. Therefore, the claimed invention as a whole was *prima facie* obvious at the time it was made.

Claims 28, 75 and 77, rejected under 35 U.S.C. § 103(a) as being unpatentable over Seitz, *Tetrahedron Letters* 40:4161-4164 (1999), in view of Thomson *et al.*, *Tetrahedron* 51:6179-6194 (1995), and Koch *et al.*, *J. Peptide Res.* 49:80-88 (1997).

As in claim 28, Seitz teaches a method for forming a support bound PNA oligomer, including dimers. In scheme 4, and description thereof, Seitz teaches coupling a first PNA monomer to a sterically hindered solid support comprising a sterically hindered acid forming cleavable linker (HYCRON resin; *i.e.*, the double bond is sterically hindered, and upon ozonolysis and peroxide treatment, alkene groups form an organic acid group), wherein the PNA monomer comprises a N-terminal protecting group. Subsequent PNA monomers are added sequentially to the resin to form a surface attached PNA oligomer. As in claims 75 and 77, Seitz teaches Fmoc/Bhoc protected PNA oligomer synthesis, wherein the nucleobase protecting group is Fmoc (page 4163, paragraph positioned directly above Scheme 4, last sentence). As in claim 76, Seitz teaches a PNA with a cytosine nucleobase.

Although Seitz teaches certain important reaction conditions, Seitz does not explicitly provide the reaction times for the deprotection step, such as Applicants about 1 to about 2 minutes and reference to cyclization, found in claim 28.

Thomson, a teaching referenced by Seitz (reference number 11), teaches PNA oligomer synthesis on resins. Thompson teaches a deprotection step that is carried out at 3 x 5 minutes.

Koch, who also references Thomson (reference number 11), teaches that when using protected amines in PNA chemistry, careful selection of the base reaction conditions must be taken into consideration to avoid cyclization (first and second columns on page 80).

One of ordinary skill in the art would have had a reasonable expectation of success in arriving at the invention as claimed because each of Seitz, Thomson and Koch, are related to the synthesis of chemically protected PNA oligomers on resins, wherein the protected oligomers are deprotected with a base in an organic solvent. One of ordinary skill in the art would have been motivated by the teachings of Thomson and Koch to ensure that cyclization was kept to reasonable levels, such as less than 50%, and would have recognized the reaction time adjustments in the range of about 1 to about 2 minutes as a matter of routine experimentation. Therefore the claimed invention as a whole was *prima facie* obvious at the time it was made.

Conclusions

No claim is allowable.

If Applicants should amendment the claims, a complete and responsive reply will clearly identify where support can be found in the disclosure for each amendment. Applicants should point to the page and line numbers of the application corresponding to each amendment, and provide any statements that might help to identify support for the claimed invention (e.g., if the amendment is not supported *in ipsis verbis*, clarification on the record may be helpful). Should Applicants present new claims, Applicants should clearly identify where support can be found in the disclosure.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Jeff Lundgren whose telephone number is 571-272-5541. The Examiner can normally be reached from 7:00 AM to 5:30 PM.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, James Schultz, can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

JSL



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